CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-241

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.: **3** 2. ANDA: **75-241**

3. NAME AND ADDRESS OF APPLICANT:
Abbott Laboratories
200 Abbott Park Road
D-389 AP30
Abbott Park, IL 60064

4. LEGAL BASIS FOR SUBMISSION:
Lasix® Hoechst-Roussel Pharmaceuticals

5. SUPPLEMENTS: **N/A**

6. PROPRIETARY NAME: **N/A**

7. NONPROPRIETARY NAME: **Furosemide Injection**

8. SUPPLEMENTS PROVIDE FOR: **N/A**

9. AMENDMENTS AND OTHER DATES:

04-14-99	**Telephone Amendment**
03-05-99	**Minor Amendment**
03-02-99	**T-Con with firm**
09-09-98	**Major Amendment**
10-03-97	**Original Submission**
12-01-97	**T-con with firm**
12-03-97	**New Correspondence**
12-09-97	**Acceptable for filing - email**
12-10-97	**Submission of EER**
12-10-97	**Acceptable for filing letter**
01-05-98	**Labeling Review - Deficient**
02-17-98	**Bio Review - Acceptable**

10. PHARMACOLOGICAL CATEGORY: 11. R_x or OTC:
Diuretic and renal tubule inhibitor **R_x**

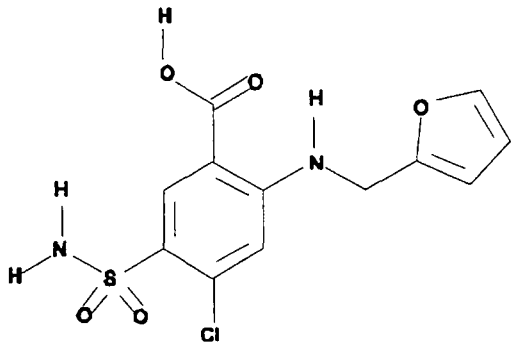
12. RELATED IND/NDA/DMF(s): **NDA 19-445/S-002 and ANDA**

13. DOSAGE FORM:
IV and IM (terminally sterilized, non-pyrogenic solution, which contains no preservative).

14. POTENCY: **10 mg/mL**

15. CHEMICAL NAME AND STRUCTURE:
Furosemide USP
$C_{12}H_{11}ClN_2O_5S$; M.W. = 330.74, CAS [54-31-9]

4-Chloro-*N*-furfuryl-5-sulfamoylanthranilic acid



16. RECORDS AND REPORTS: **N/A**

17. COMMENTS:

1. The statistical review provided on page 22 for Breakloose and Extrusion forces for Plastic _ ,yringes states that except for the breakloose results for pH 3 water, the breakloose and extrusion results changed significantly from interval to interval. Please explain how this variability will impact the functionality of the syringe to deliver the intended volume. In addition, please define the terms "breakloose" and "extrusion forces" as they apply to this study and also define the syringe system that was being tested.

Response: Breakloose force is defined as the force required to initiate the movement of the plunger. Extrusion force is the force required to sustain movement of the plunger through the delivering the contents of the syringe.

The firm indicates that although the values are statistically different, but this does not necessarily mean that they have any practical impact on the functionality of the syringe. Thus, these differences are not functionally different. (Satisfactory)

2. With respect to the graduation accuracy report (page 39 of this submission), please specify the following: (a) the type and make of syringes used in the study (b) How do these results meet the USP requirements for volume of injection in containers? From the data provided, some of the

volumes delivered may be less than the labeled amount. (C) This report studied the accuracy of delivery based on label placement, please summarize the delivery of the syringes without reference to the placement of the label. (d) Please provide the test methodology and actual data for this study.

Response: The syringes (5-mL and 10-mL)used in the study were made of . The firm ensures that the product meets the container requirements for USP (Not less than the labeled volume) by appropriate manufacturing controls and confirmed by finished product testing. The data provided (Exhibit II) indicates that the values for the average error and standard deviation for the target dose and partial dose are both less than (Note: In the 10-mL study, high position indicated that the label was moved toward the flange end of the syringe. Current production specifications allow only inch movement in this direction, reducing the associated error by about Satisfactory

4. Please revise the specification for the particulate matter test at release and on stability and establish limits for this test. In addition, please indicate the levels of particles that would require an action to occur and explain what is done with this information if the product fails.

Response: Abbott's will test for particulates in the syringe product. However, the firm indicates that the pre-filled syringes are exempted from the USP particulate-testing requirement. The firm provided testing criteria that are consistent with USP limits. A copy of the method has been provided.

Comment: In USP 23 General Chapter <788> Particulate Matter in Injections (Supplement 5, Pg. 3476), "pre-filled syringes and cartridges are exempt from these requirements, as are products for which the individual monograph specifies that the label states that the product is to be used with a final filter." (Satisfactory)

3. Your references to the approved extractables testing for NDAs 19-445 and and ANDA are acknowledged. Please explain how this study relates to extractables for this product. Although, the container closure system has been

previously approved, there is no information provided to this application regarding extractables with this drug product's vehicle. Please provide this information to the application.

Response: The states that a comprehensive study proposal was reviewed by Mr. Stanley Kock (Surgical and Dental Products Division of the FDA) for the use of family of solutions to cover ten variety of drug products. Extractable studies were conducted to monitor for the potential extractables DBF and NA-11 in a family of solutions consisting of 75% Iopamidol, 50% Magnesium Sulfate, WFI (pH 3.0, pH 6.0, and pH 9.5). The test period lasted two years. This study provided the basis for nine other drug products, packaged in the syringe in 1998.

The firm claims that Furosemide Injection would be bracketed by the above family of solutions. (Note: The vehicle for the furosemide injection is a saline solution pH adjusted to 8.0 - 9.3.) the firm states that the same bracketing has previously been approved by OGD (ANDA Iopamidol Injection, ANDA Verapamil Injection and ANDA 'Lidocaine HCl Injection. (Satisfactory)

6. Please revise the stability protocol to specify that the first three lots of each fill/strength of each container closure system will be placed on stability and annually thereafter, one lot of each strength/fill in each container closure system will also be placed on stability. In addition, please specify that the expiration date for the product may be extended with the supporting data from three consecutive lots of each strength/fill of product in each container/closure system.

Response: The marketed product stability protocols were changed and copies are provided. (Satisfactory)

7. Your reference to ANDA isted in the response to comment 12 of the July 9, 1998 amendment is not correct. Please provide a correct reference.

Response: The correct reference is Iopamidol Injection. (Satisfactory)

18. CONCLUSIONS AND RECOMMENDATIONS: **APPROVABLE**

19. REVIEWER: David J. Cummings DATE COMPLETED: 04/23/99

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Contain Trade Secret, Commercial/Confidential Information and are not releasable.

4/23/99
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